Title of Challenge: Inhalation Translation

Background

Chronic inflammatory diseases of the airways, such as asthma and chronic obstructive pulmonary disease (COPD), remain areas of considerable unmet medical need. Few new drugs have made it to the clinic during the past 50 years, with many that perform well in preclinical animal studies failing in humans owing to lack of safety and/or efficacy. The failure to translate promising drug candidates from animal studies and other preclinical assays to humans has led to questions about the utility and relevance of current preclinical models and demand for more predictive tools.

Inhaled therapies for asthma were first developed in the 1950s and remain the preferred route of administration for treating the disease because they enable the topical delivery of minute but therapeutically effective doses of drug into the airways eliciting local effects within the lungs. The improved pharmacokinetic profiles and reduced side effects of inhaled therapies also make this a promising route of administration for non-pulmonary indications, e.g. diabetes. Pharmaceutical companies are investing in dry powder delivery devices for inhalation therapies as they offer many advantages over aerosolised solutions. However, preclinical development of inhaled dry powder therapies presents a number of challenges. These can arise through both the poor understanding of the lung response to dry powders and the current inability to effectively monitor efficacy, making dose selection and duration of action assessment particularly challenging.

Animals (mainly rodents) are pre-dosed with candidate drugs and then exposed to a pro-inflammatory challenge (e.g. lipopolysaccharides (LPS)). Lung biopsies or lavage are then examined at defined time points to assess both anti-inflammatory efficacy and toxicity of the compound. This process has a number of limitations and uses a significant number of animals.

One of the difficulties in assessing inhaled drugs in toxicity studies is the alveolar macrophage response and its relevance to safe dosing in the clinic. One characteristic of inhaled dry powder toxicity studies is the appearance of foamy macrophages (FM), but it is unclear if this is due to general particulate overload or a pharmacologically-driven adverse event. This is further complicated when subtle changes in macrophage numbers, appearance and activation are observed, as they may represent an adaptive response to the dosed material, or the initial stages of an adverse health effect. The inability to discriminate between such responses triggers additional *in vivo* assessments to determine whether there are secondary consequences of FM appearance, such as inflammation, to make go/no-go decisions on candidate drugs. To improve inhaled drug development, a better understanding is required of FM biology, the influence of different macrophage phenotypes on other lung cells and species differences. This knowledge base would reduce costly and repetitive toxicological studies in animals required to optimise safe doses.

3Rs benefits

As an example, a single biology efficacy study using six groups of animals, pre-dosed at a single level over a partial time course requires approximately 60 animals. This might be repeated three times, requiring 180 animals, although the final figure is likely to be many more when full time courses, control groups and multiple studies are taken in to consideration.

Successfully solving this challenge would have the following 3Rs benefits:

- Ability to evaluate toxicity and efficacy longitudinally in the same animal, potentially reducing animal use by up to 90% at certain stages of drug discovery and development
- More reliable and less variable data resulting in fewer animals being used

- Earlier go/no-go decisions can be made on drug candidates therefore requiring fewer regulatory toxicity studies in candidates that will fail later in development
- Potential for similar 3Rs benefits to translate to other therapeutic areas where inhaled therapy could be used (e.g. diabetes, heart failure, oncology)

Need for collaboration

Solving this Challenge will require (i) advanced assay platforms, imaging technology, and histological expertise for longitudinal assessment of inflammation and FM response, and (ii) development of novel probes and reporter systems, improved contrast agents, novel biomarkers to monitor inflammation and FM related toxicity. The multidisciplinary nature means that expertise from a number of different sectors will be needed to provide a solution and input from the integration of diverse disciplines such as chemistry, biology, pathology and imaging specialists will be critical.

Overall aim

To enable the longitudinal and non-invasive assessment of inflammation and FM toxicity in the same animal through a series of dose-escalation stages. This will require (i) the development of translational tools to assess FM modulation and inflammation in a longitudinal manner in rodent lungs (primarily the rat) and (ii) better insight into FM status and functionality as a response to drug inhalation.

Key deliverables

- A non-invasive approach with the following characteristics is required:
- Ability to monitor how the rodent lung responds to inhaled drugs to demonstrate a decrease/inhibition of an induced pro-inflammatory process over a defined dose range
- Allows monitoring of lung responses (e.g. gaseous exchange) to inhaled drugs, at toxicological doses for dosing periods of sufficient length to support human clinical studies
- Can demonstrate that small changes to airway macrophage populations (including foamy macrophages) are either non-adverse or adverse in nature, allowing clear go/no-go criteria to be established

Phase 1

- The development/application of novel *in vitro, ex vivo* and/or *in vivo* approaches to better understand FM biology*. In vitro/ex vivo* approaches must go beyond those already available and incorporate the latest advances in microfluidic and tissue engineering technologies. *In vivo* approaches must use the absolute minimum number of animals monitored over time. Applicants must demonstrate:
    - Identification of potential markers of FM presence and their functional state
    - Development of novel biomarkers that demonstrate a change in the activation state of FM but which do not induce any cellular activation in the lung in their own right
    - Demonstration that changes in functional state of FM are recapitulated in healthy lung macrophages and proof that the changes translate across species
    - Use of the identified biomarkers to understand and characterise the occurrence of FM following particulate dry powder delivery in rodents
    - Demonstration of a relationship or collaboration with the expertise needed for Phase 2

Phase 2

Essential

System to simultaneously monitor disease progression/efficacy of compound, drug deposition and retention and FM presence longitudinally and non-invasively in the same animal without impacting on animal welfare (e.g. use of gel, requirement for shaving, etc.).

Desirable

- Development of non-invasive approaches to quantitate increased influx of mononuclear cells into the rodent lung following administration of a pro-inflammatory stimulus (eg LPS) and ultimately the resolution of such a response
- Define the FM macrophage phenotype that indicates an adverse response
- Measure of inflammation that is transferable across a range of inflammatory stimuli
- Non-invasively define the rodent lung response to inhaled pharmaceutical agents that have known detrimental effects upon lung pathology compared to negative controls
- Improve understanding of:
    - The timeframe over which FM responses occur
    - The influence of compounds with different pharmacology on FM biology (vs particulates)

Sponsors In-kind contributions

Phase 1

Advice and guidance on industry requirements and current knowledge

Phase 2

- *In vivo* validation of functional markers*
- Assessment of new technology
- Expertise in respiratory disease and relevant efficacy and toxicity readouts
- Access to compounds

Duration

Phase 1: six months. Phase 2: up to three years

Budget

Phase 1: up to £100K. Phase 2: up to £1 million

Sponsors

Pfizer, Huntingdon Life Sciences and GSK

*All animal studies will be ethically reviewed and carried out in accordance with national regulatory and legal requirements and company policies on the care, welfare and treatment of animals.